PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Efficacy of open dialogue about complementary and alternative medicine compared with standard care in improving quality of life in patients undergoing conventional oncology treatment (CAMONCO 2): protocol for a randomized controlled trial
AUTHORS	Stie, Mette; Delmar, Charlotte; Nørgaard, Birgitte; Jensen, Lars Henrik

VERSION 1 – REVIEW

REVIEWER	FENG, Yibin The University of Hong Kong, School of Chinese Medicine
REVIEW RETURNED	21-Jan-2022

GENERAL COMMENTS	1.As you mentioned in the Methods and analysis, I have a question about the time you set. Why do you measure the primary outcome at eight weeks after enrollment? Could you provide supporting evidence? 2.Why choose patients diagnosed with primary cancer or recurrence within the last three months? please give a reason. 3.Why consent must be given within 12 weeks from treatment start as mentioned in Recruitment, i.e. at the fourth cycle of treatment at the latest? Please give a reason. 4.What if the patient disclose their allocation status at the follow-up visits? Are there any corresponding countermeasures in the part Blinding? 5.As you mentioned in the part Intervention group: OD-CAM, if the number of OD-CAM sessions depends on the individual patient, will it become a variable which cause errors due to different treatment intentions of patients? How to reduce test errors? 6.Why choose eight weekst1 after enrollment to measure the primary outcome and choose 8t1, 12t2 and 24t3 weeks after enrollment to measure the secondary outcome? Perform a reason?

REVIEWER	Stub, Trine UiT, The Arctic University of Norway, The National Research Center in Complementary and Alternative Medicine-NAFKAM,Department of community medicine
REVIEW RETURNED	09-Feb-2022

GENERAL COMMENTS	Study protocol: a randomized controlled trial comparing the efficacy of open dialogue about complementary and alternative medicine

	(OD-CAM) with standard care (SC) in improving quality of life in patients undergoing conventional oncology treatment (CAMONCO 2) Thank you for the opportunity to review this manuscript. This study protocol aims to investigate the effect of an open dialogue about CAM compared to standard care in an oncology setting in Denmark. The design is a randomized controlled trial. The manuscript is interesting, but I have some suggestions that I hope will improve the quality of the trial. Title: and is missing between complementary and alternative medicine in the title. Generally, throughout the manuscript it is a tendency to not complete the sentences. For example, in the abstract Introduction: Line 10…. but CAM might also cause symptoms and side-effects. An option is to write but CAM may also cause symptoms and side-effects such as headache and fatigue. It is however not recommended to use the term side-effects in a CAM context. A side effect is an effect produced by an agent, other than the intended. The definition has been criticized since it is quite related to the immediate drug reaction and may therefore be interpreted as minimizing the potential hazard of the pharmacological product. The term adverse effect is more suitable for CAM modalities as it is defined as an adverse outcome that can be attributed to some action of a drug or an intervention. The term encompasses all unwanted effects, without making assumptions about their mechanisms. The term covers, a broad spectrum of potential risks and thus include more sources of risk than merely those related to drugs. A broader definition of risks is appropriate in complex treatment situations such as in complex lifestyle-oriented intervention programs and CAM. I suggest therefore to use the term adverse effects throughout the manuscript. Introduction I think it is relevant to include a definition of CAM and distinguish between alternative and integrated medicine. In addition, please include information about prevalence of CAM use internationally and in Denmark. I would also be interesting to know the most used CAM modality in Denmark generally and more specially for cancer. Line 10 p 4: the authors states that in the management of cancer related symptoms and side-effects CAM is relevant…… This is unclear to me, side-effects of what? Line 13, p 5: the authors write: We tested the effects of OD-CAM on adverse events… adverse event of what? Conventional cancer treatment or CAM? Please clerify. Line 15, p5, ….and the degree of side-effects. Please clarify, the side-effects of what? See also my comments about the terminology. Line 30, p5: I suggest moving the sentence that start with, Based on the interviews…… to after OD-CAM (line17). One cannot draw any conclusion about effect from a qualitative study. The design is appropriate when investigators want to map the experiences of a group of participants. So please rewrite the sentence above. For example: Based on data from the interview study, the participants found that OD-CAM was beneficial for reducing uncertainty……. The terminology commonly used in CAM literature about decision regret of conventional cancer treatment is decline or delay conventional cancer treatment (Line 14, p6, the aim). Methods and analysis

	Design Please se my comments above about the interview study and rewrite this paragraph accordingly (line, 17-18, p 6). Line 16, …CAMONCO 2 investigates patient-reported quality of life as opposite to side-effect, symptoms, and patient satisfaction. This sentence is unclear, side-effects of what? Settings Please add some information about the health care system in Denmark. Is CAM a part of the official health care system or is it practiced outside this system and paid out of pocket? Participants Please add age of adult patients. Inclusion and exclusion criteria Please include exclusion criteria in this paragraph Add the following inclusion criteria: signed informed consent to participate form Intervention group: Line 13, p 9: Please use CAM modalities instead of CAM treatments Line 15, p 9: Please add, what are these recommendations? (Schofield et al.'s recommendations) Table 2: Please include dates for when these events are going to happen Statistical plan The authors are referring to the null hypothesis. However, I cannot see that the authors have added any study hypothesis for the trial. Please add them after the aim of the study. Discussion and conclusion Line 10, p 21, replace randomized controlled study with randomized controlled trail. References Something is wrong with reference nr 32 (need to add a comma in the endnote program in order to show the authors name).

VERSION 1 – AUTHOR RESPONSE

Response to Reviewer 1:
Reviewer: 1 [Dr. Yibin FENG, The University of Hong Kong Comments to the Author:
PLEASE ALSO SEE ATTACHED FILE FOR COMMENTS ON SPIRIT CHECKLIST]
Response: Thank you for the comments regarding the SPIRIT checklist: We have reported all SPIRIT requirements within the manuscript and indicated in the checklist where the information is reported. We hope that the SPIRIT checklist is now filled out sufficiently.

1. As you mentioned in the Methods and analysis, I have a question about the time you set. Why do you measure the primary outcome at eight weeks after enrollment? Could you provide supporting evidence?
Response: Thank you for highlighting this important question. We agree that explanation about time point is important. Thus, we have elaborated the time point for primary outcome measure in the Design section.

2. Why choose patients diagnosed with primary cancer or recurrence within the last three months? please give a reason.
Response: Thank you for asking this very relevant question. We acknowledge that all patients (regardless of time of diagnosis or recurrence) potentially will benefit from OD-CAM. However, being diagnosed with cancer initiates CAM use, which makes patients´ need for guidance in safe and healthy use of CAM crucial. Furthermore, we have outlined our hypothesis in the aim section- our

hypothesis is that patients will benefit for OD-CAM when it is integrated early in the treatment trajectory. We hope that this clarifies our choice of inclusion criterion

3. Why consent must be given within 12 weeks from treatment start as mentioned in Recruitment, i.e. at the fourth cycle of treatment at the latest? Please give a reason
Response: As described in the former response, our hypothesis *is that patients benefit from OD-CAM when it is integrated early in the treatment trajectory. Thus, consent must be given early/within 12 weeks.*

4. What if the patient disclose their allocation status at the follow-up visits? Are there any corresponding countermeasures in the part Blinding?
Response: Thank you for reminding us that this is truly a non-blinded study. We have deleted the sentence and rephrased the Blinding section.

5. As you mentioned in the part Intervention group: OD-CAM, if the number of OD-CAM sessions depends on the individual patient, will it become a variable which cause errors due to different treatment intentions of patients? How to reduce test errors?
Response: Thank you for reminding us to consider this potential error. If there is a great variety in number OD-CAM sessions we will do sub-group analysis. We have included a sentence about this in the end of the Statistical methods section

6. Why choose eight weekst1 after enrollment to measure the primary outcome and choose 8t1, 12t2 and 24t3 weeks after enrollment to measure the secondary outcome? Perform a reason.
Response: We believe that we have explained the timepoint of primary outcome in comment 1. Regarding timepoint of secondary outcome: These timepoiont were chosen because in the CAMONCO 1 study, we found significant differences in QoL at 12 and 24 weeks.

Reviewer: 2
Miss Trine Stub, UiT, The Arctic University of Norway, Wake Forest School of Medicine Comments to the Author:

Bmjopen-2121-059960
Study protocol: a randomized controlled trial comparing the efficacy of open dialogue about complementary and alternative medicine (OD-CAM) with standard care (SC) in improving quality of life in patients undergoing conventional oncology treatment (CAMONCO 2)

Thank you for the opportunity to review this manuscript. This study protocol aims to investigate the effect of an open dialogue about CAM compared to standard care in an oncology setting in Denmark. The design is a randomized controlled trial. The manuscript is interesting, but I have some suggestions that I hope will improve the quality of the trial.

1. Title: and is missing between complementary and alternative medicine in the title.
Response: Thank for this observation: The title has been changed according to Editors comment 1.

1. Generally, throughout the manuscript it is a tendency to not complete the sentences. For example, in the abstract.

Response: Thank you for this thorough observation. We have re-read the whole manuscript and completed sentences.

1. Introduction: Line 10…. but CAM might also cause symptoms and side-effects. An option is to write but CAM may also cause symptoms and side-effects such as headache and fatigue.

Response: Thank for this relevant suggestion. We have added you suggestion to the sentence

1. It is however not recommended to use the term side-effects in a CAM context. A side effect is an effect produced by an agent, other than the intended. The definition has been criticized since it is quite related to the immediate drug reaction and may therefore be interpreted as minimizing the potential hazard of the pharmacological product. The term adverse effect is more suitable for CAM modalities as it is defined as an adverse outcome that can be attributed to some action of a drug or an intervention. The term encompasses all unwanted effects, without making assumptions about their mechanisms. The term covers, a broad spectrum of potential risks and thus include more sources of risk than merely those related to drugs. A broader definition of risks is appropriate in complex treatment situations such as in complex lifestyle-oriented intervention programs and CAM. I suggest therefore to use the term adverse effects throughout the manuscript.

Response: Thank you for highlighting this distinction. We have replaced side-effects with adverse events when it is related to conventional treatment (this is the recommend term in conventional context) and replaced side-effects with adverse effects when it is related to CAM throughout the manuscript

1. Introduction

I think it is relevant to include a definition of CAM and distinguish between alternative and integrated medicine.
In addition, please include information about prevalence of CAM use internationally and in Denmark. I would also be interesting to know the most used CAM modality in Denmark generally and more specially for cancer.
Response. Thank you for these relevant suggestions. In the introduction section we have included a definition of CAM and integrative oncology. Also we have included information about use of CAM among patients with cancer. We acknowledge that use of CAM in general is interesting. However, this study exclusively includes patients undergoing cancer treatment and we know from other studies that CAM use is either initiated or increased in relation to the cancer diagnosis.

1. Line 10 p 4: the authors states that in the management of cancer related symptoms and side-effects CAM is relevant…… This is unclear to me, side-effects of what?

Response: We agree that this sentence is a little implicit. Thus, we have rephrased the sentence and added: adverse events to conventional cancer treatment…

1. Line 13, p 5: the authors write: We tested the effects of OD-CAM on adverse events… adverse event of what? Conventional cancer treatment or CAM? Please clerify.

Response: As your comment above, we agree that this sentence also is a little implicit. Thus, we have added that it is adverse events of conventional cancer treatment.

1. Line 15, p5, ….and the degree of side-effects. Please clarify, the side-effects of what? See also my comments about the terminology.

Response: Again, as your comment above, we have added that it is adverse events of conventional cancer treatment

1. Line 30, p5: I suggest moving the sentence that start with, Based on the interviews…… to after OD-CAM (line17).

One cannot draw any conclusion about effect from a qualitative study. The design is appropriate when investigators want to map the experiences of a group of participants. So please rewrite the sentence above. For example: Based on data from the interview study, the participants found that OD-CAM was beneficial for reducing uncertainty…….
Response: Thank you for highlighting this important detail and for the suggestion. We have rephrased the sentence

1. The terminology commonly used in CAM literature about decision regret of conventional cancer treatment is decline or delay conventional cancer treatment (Line 14, p6, the aim).

Response: We are aware that the terminology commonly used in CAM literature about decision regret of conventional cancer is decline or delay. However, in this study patients have not declined or delayed the conventional treatment. In fact, it is an inclusion criterion that they are receiving conventional cancer treatment. Thus, we investigate whether OD-CAM integrated in conventional oncology treatment potentially affects patient reported decision regret regarding the conventional treatment.

Methods and analysis

Design

1. Please se my comments above about the interview study and rewrite this paragraph accordingly (line, 17-18, p 6).

Response: Thank you for highlighting this again. We have rephrased the sentence.

1. Line 16, …CAMONCO 2 investigates patient-reported quality of life as opposite to side-effect, symptoms, and patient satisfaction. This sentence is unclear, side-effects of what?

Response: Thank you again for reminding us to be more clear about side-effects. We have outlined that it is adverse events of conventional cancer treatment and cancer-related symptoms. Hope that the sentence is clear now

1. Settings

Please add some information about the health care system in Denmark. Is CAM a part of the official health care system or is it practiced outside this system and paid out of pocket?
Response: Thank you for reminding us to elaborate this relevant information about the health care system and CAM. In the Setting section we have added information regarding this issue.

1. Participants

Please add age of adult patients.
Response: Thank for reminding us to add age.

1. Inclusion and exclusion criteria

Please include exclusion criteria in this paragraph Add the following inclusion criteria: signed informed consent to participate form
Response: Thank you for reminding us to add signed informed consent in the inclusion criteria and to elaborate exclusion criteria. We have rephrased the sentences in the end of the Participants section

1. Intervention group:

Line 13, p 9: Please use CAM modalities instead of CAM treatments Line 15, p 9: Please add, what are these recommendations? (Schofield et al.'s recommendations)
Response: Yes, of course it is CAM modalities and not treatments – we have changed the wording.
Regarding Schofield et al.´s recommendations: Table 1 which is a guideline in how to perform OD-CAM is inspired by Schofield. For clarification, we have added a sentence in relation to recommendations and hope it Is more clear now.

1. Table 2:

Please include dates for when these events are going to happen
Response: Thank you for reminding us to be explicit about time points of data collection. We have added the time points (8,12,24 weeks) in table 2

1. Statistical plan

The authors are referring to the null hypothesis. However, I cannot see that the authors have added any study hypothesis for the trial. Please add them after the aim of the study.
Response: Thank you for suggesting to add the study hypothesis. It is now added to the Aim section

1. Discussion and conclusion

Line 10, p 21, replace randomized controlled study with randomized controlled trail.
Resonse: study is replaced with trial

1. References

Something is wrong with reference nr 32 (need to add a comma in the endnote program in order to show the authors name).
Response: thank you for this observation. The reference is now correct.

VERSION 2 – REVIEW

REVIEWER	Stub, Trine UiT, The Arctic University of Norway, The National Research Center in Complementary and Alternative Medicine-NAFKAM,Department of community medicine

REVIEW RETURNED	11-Mar-2022

GENERAL COMMENTS	The authors have made the changes according to mine last comments. I have no further comments.